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**Metabolic and structural skeletal muscle health in systemic lupus erythematosus related fatigue: a multi-modal magnetic resonance imaging study**

Sai Man Cheung MSc<sup>1</sup>, Karen Keenan PhD<sup>1</sup>, Nicholas Senn MSc<sup>1</sup>, Gayle Hutcheon BSc<sup>2</sup>, Kwokshing Chan MSc<sup>1</sup>, Lars Erwig MD PhD<sup>1,3</sup>, Andrew Schrepf PhD<sup>4</sup>, Paula Dospinescu MD<sup>2</sup>, Stuart Gray PhD<sup>5</sup>, Gordon Waiter PhD<sup>1</sup>, Jiabao He PhD<sup>1</sup>, Neil Basu MD PhD<sup>5</sup>

<sup>1</sup>University of Aberdeen, School of Medicine, Medical Sciences and Nutrition, Aberdeen, UK

<sup>2</sup>NHS Grampian, Department of Rheumatology, Aberdeen, UK

<sup>3</sup>GlaxoSmithKline, Medicines Research Centre, Stevenage, UK

<sup>4</sup>University of Michigan, Chronic Pain and Fatigue Research Center, Ann Arbor, USA

<sup>5</sup>University of Glasgow, Institute of Infection, Immunology and Inflammation, Glasgow, UK

Corresponding author:

Neil Basu MBChB PhD, Institute of Infection, Immunology and Inflammation, University of Glasgow, Glasgow, G12 8TA. E-mail: neil.basu@glasgow.ac.uk

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**Abstract**

Objective: This study aimed to investigate the potential structural and metabolic role of skeletal muscle in SLE related fatigue.

Methods: A case control, multi-modal MRI study was conducted. Cases were inactive SLE patients who reported chronic fatigue. Controls were age/sex matched healthy members of the general population. Participants were clinically characterised and then underwent a 3T whole body MRI scan. Resting and dynamic <sup>31</sup>Phosphorous Magnetic Resonance Spectroscopy (MRS) of the calf muscles was applied from which phosphocreatine recovery half time (PCr), a marker of mitochondrial dysfunction, was computed. In addition, microstructural sequences (T1-weighted anatomical images, T2 mapping and diffusion tensor imaging) were acquired. Descriptive statistics evaluated group differences and within case physical fatigue correlations were explored.

Results: Of the 37 recruits (mean age= 43.8 years, 89.2% female), cases (n=19) reported higher levels of physical fatigue, pain, depression and sleep disturbance compared to the control group ( $p < 0.0001$ ). PCr was greater ( $p = 0.045$ ) among cases ( $33.0 \pm 9.0s$ ) compared to controls ( $27.1 \pm 6.6s$ ). No micro-structural group differences were observed. Within cases, physical fatigue did not correlate with PCr ( $r = -0.28$ ,  $p = 0.25$ ).

Conclusion: We report preliminary data evidencing greater skeletal muscle mitochondrial dysfunction among fatigued SLE patients compared to healthy controls.

**Significance and innovations:**

- SLE related fatigue does not appear to be implicated with abnormal skeletal muscle micro-structure
- SLE patients evidence higher levels of skeletal muscle mitochondrial dysfunction

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## Introduction

Systemic lupus erythematosus (SLE) patients consider fatigue to be one of the most pervasive and disabling aspects of their disease. As many as 85% report significant levels of fatigue(1), a prevalence greater than that observed in the general population and commoner inflammatory rheumatic disorders(2). Moreover, its impact permeates all aspects of life as reflected by its strong associations with impaired quality of life(3) and work disability(4). Despite these significant consequences, little is understood about this symptom. The major challenge in clinical practice is to deliver therapeutic options to those patients whose disease is otherwise in remission and for whom no other reversible causes are apparent(5).

Patients describe multiple dimensions of fatigue and therefore its aetiology is likely to be complex. The predominance of both physical and mental fatigue (6) alludes to a mixture of peripheral and central mechanisms. In terms of investigating the former, skeletal muscle dysfunction has previously been associated with SLE related fatigue(7), although no studies have investigated whether this observation is underpinned by pathological abnormalities within the muscles themselves.

Developments in magnetic resonance (MR) imaging technology offer a non-invasive opportunity to comprehensively quantify skeletal muscle pathology at both metabolic and structural levels. For example, <sup>31</sup>P MR Spectroscopy (MRS) allows for the direct measurement of altered metabolic activity, such as levels of phosphocreatine (PCr), in vivo during physical activity and has previously signalled dysfunction in the muscles of chronic fatigue syndrome (CFS) populations(8). In contrast to CFS, there is some histological evidence that at least selected SLE patients evidence structural abnormalities in their skeletal muscle(9). Novel methods such as diffusion tensor imaging (DTI) are sensitive to pathological abnormalities associated with overall cell geometry and oedema(10, 11). In addition to high resolution MRI for the quantification of muscle volume, T<sub>2</sub> mapping highlights oedema, while Dixon MRI allows quantitative measurement of fat infiltration. To our knowledge, no

study has yet to contemporaneously employ these methodological advances in order to investigate SLE.

We aimed to investigate the differences between the metabolic and structural features of skeletal muscle among SLE patients with idiopathic fatigue and healthy controls using multi-modal MR muscle imaging

## **Patients and Methods**

A case-control study was conducted. Subjects were invited to undertake a multi-modal MRI scan of their calf muscles alongside the collection of clinical data. The East Midlands - Leicester Research Ethics Committee (ref: 15/EM/0418) approved the study and written informed consent was obtained from patients according to the Declaration of Helsinki.

### *Subjects*

Cases were patients with SLE, classified according to the 1997 American College of Rheumatology (ACR) criteria(12), attending secondary care clinics in NHS Grampian. To be eligible, they required to 1) report chronic (>3months), clinically important fatigue (defined as a score of >3 on the Chalder fatigue binary scale (CFS)(13)) 2) experience reduced muscle strength (item 6 of CFS) and 3) have inactive SLE, defined as a British Isles Lupus Assessment Group 2004 score=0 (excluding the fatigue-constitutional domain)(14). In addition, patients were excluded if they evidenced any past history of clinically diagnosed myositis or alternative medical explanations for their fatigue (symptomatic cardio-respiratory disease, a history of cancer in the previous 5 years, unstable thyroid disease, moderate to severe chronic kidney disease, moderate to severe anaemia, beta-blocker prescription, fibromyalgia).

Controls, recruited by local advertising, were healthy (no relevant past medical history) participants who did not report clinically important fatigue ( $CFS \leq 3$ ) or reduced muscle strength (item 6 of CFS). They were approximately matched to cases by age and sex. In order to offset potential confounding due to deconditioning, they additionally required to be sedentary, defined as those having a desk job and undertaking <3 hours of physical activity per week(8).

Any potential case or control with a contra-indication to MRI (e.g. pacemaker *in situ*) was excluded.

### *Clinical characterisation*

Eligible cases underwent a clinical evaluation which included an assessment of disease damage (SLICC)(15), previous organ involvement and disease duration. Erythrocyte sedimentation rate, serum creatinine and creatine kinase were measured in both cases and controls.

All subjects completed a self-report questionnaire which included validated measures and known confounders of fatigue:

a) Chalder Fatigue Scale is one of the most commonly employed measures of fatigue, it has been found to be both feasible and acceptable in SLE(16). Of the 11 questions, 7 specifically examine physical fatigue and are Likert scored (range 0–21) with high scores indicating high levels of physical fatigue.

a) Hospital Anxiety and Depression Scale is a validated 14-item tool for assessing anxiety and depression in SLE and the general population(17). It also employs a Likert-style scoring system (range 0–21 for each domain).

b) Pain Severity was measured using a 0-10 numerical rating scale

c) Jenkin's sleep scale is known to perform well in both non-clinical and clinical populations, succinctly quantifying key sleep dysfunction domains: difficulties in sleep onset and maintenance, early waking and non-restorative sleep. The domain scores are totalled (range 0–20), with higher scores indicating greater sleep disturbance(18).

Finally, both cases and controls underwent the Siconolfi Step Test. This measure of aerobic fitness (a putative confounder) has been validated in SLE patients(19). It involved patients stepping up and down from a 10 inch bench for 3 mins at a rate of 17 steps per minute (guided by a metronome). Heart rate was monitored and the protocol stopped if 65% of the predicted (220 minus age) heart rate was exceeded. If not reached, then a second (26 steps per minute) and third stage (34 steps per minute) was performed, with 1 minute rest between stages. Maximal oxygen uptake ( $VO_{2max}$ ) was then estimated using the formulae described by Siconolfi et al(20).

#### *MRI Acquisition*

Images were acquired on a 3T whole body MRI scanner (Achieva TX, Philips Healthcare, Best, Netherlands) using the body coil for transmission and an 8-channel knee coil as the receiver. In one SLE patient and two healthy controls, the diameter of lower leg was too large for the knee coil and in these cases a 2-channel flex-M receiver coil was used. The imaging volume was centred at the thickest part of the right calf, with the subject in supine position.

T1-weighted anatomical images were acquired using a standard sequence with repetition time (TR) of 2700 ms, echo time (TE) of 55 ms, field of view (FOV) of  $160 \times 160 \text{ mm}^2$ , matrix size of  $160 \times 160$ , and 48 slices of 1.5 mm thickness.

T2 mapping was performed using a gradient and spin echo (GRASE) sequence with TR of 3137 ms, 12 equally spaced echoes from TE of 10 ms to 120 ms(21, 22). Diffusion tensor imaging (DTI) was acquired using a single-shot pulsed gradient spin echo (PGSE) sequence with TR/TE of 2000/53 ms(11, 23), 32 diffusion directions, diffusion weighting of  $400 \text{ s/mm}^2$  and 2 averages(24). Fat mapping was performed using multi slice multi-echo spoiled gradient-echo sequence, with TR of 20 ms, 16 equally spaced echoes from TE of 1.14 ms to 18.24 ms,  $3^\circ$  flip angle(25, 26). For T2 mapping, DTI and fat mapping, the imaging volume was set to FOV of  $192 \times 192 \text{ mm}^2$ , and 12 transverse slices of 6 mm thickness. The matrix size was set to  $128 \times 128$  for T2 and fat mapping, and  $64 \times 64$  for DTI to ensure adequate signal-to-noise ratio(24).

$^{31}\text{P}$ -MRS was acquired from a 14 cm diameter  $^{31}\text{P}$  coil positioned underneath the thickest part of the calf, using 1D ISIS sequence with the detection slab covering the posterior portion of the calf(27). Dynamic spectra were acquired with TR of 5 s and 108 dynamics(28), while the subject concurrently performing plantar flexion exercise protocol at 20% maximal voluntary contraction (MVC) in synchrony to an audio metronome prompt at 35 bpm. Isometric MVC of the right calf with 90 degree plantar ankle flexion for each subject was measured (KinCom500H dynamometer, KinCom, East Ridge, TN, USA). Measurements at 2 min intervals were performed until the difference between the last two measures were less than 5% of their average, normally 3-4 repetitions were performed. The highest of the last two measures was taken as the MVC(29). The exercise paradigm contained a 2 min baseline followed by two 8 min cycles, where each cycle was composed of a 3 min exercise before a 5 min recovery period.

### *Image Analysis*

The  $^{31}\text{P}$  spectra were processed in jMRUI v3.0 software(30), and PCr half time computed from the PCr time course in the post exercise recovery period as an indicator of muscle energetics(31). DTI analysis was performed in FSL software (FMRIB, Oxford, UK), to derive metrics maps of mean diffusion (MD), radial diffusivity (RD) and fractional anisotropy (FA) (23) as indicators of muscle integrity(24). In five subjects, images suffering from motion artefact resulting in failure of the motion correction algorithm were identified and removed before the calculation of diffusion metrics. T2 maps were computed using in-house software in MATLAB (Mathworks, Natick, USA), following standard procedures(21). Fat fraction maps, as the ratio between fat and the sum of fat and water images, were computed using the ISMRM Fat-Water Toolbox in MATLAB(32). Fat and water were



separated using a multi-step fitting approach(33), incorporating a multi-frequency fat spectrum model(34, 35). To avoid confounding factors, patients with non-compliance to the exercise protocol were excluded from the PCr halftime analysis; patients using the flex-M coil or showing severe image artefact were excluded from corresponding image analysis (Table 2).

Regions of interest (ROI) were manually drawn by a single operator in MRICron (South Carolina, USA) on the central 10 slices of the image acquired at a TE of 10ms from T2 mapping, to delineate soleus and excluding subcutaneous fat or blood vessels. The binary masks were subsequently applied on maps of T2, MD, FA, RD and fat fraction to generate the average value. Muscle volumes of soleus was also quantified as the cross-sectional area on the central slice of T1-weighted anatomical image(36).

#### *Power calculation*

Eighteen subjects per group sufficiently affords over 80% power to detect an effect size of 0.85 with a measurement error of 30% at an alpha of 0.05 (as measured by PCr recovery half time)

#### *Statistical Analysis*

Clinical parameters were expressed using simple descriptive statistics with case control comparisons made using Chi squared tests for categorical variables and t-tests for continuous variables.

To investigate the role of skeletal muscle energetics in SLE, the case control comparison of PCr half time was performed using a t-test. To examine the role of muscle microstructure integrity and muscle volume in SLE, the case control comparison of MD, FA, RD, T2 and fat fraction, as well as the cross sectional area, were performed using t-tests.

Within case Pearson correlations were conducted using STATA v12.1 (Stata, College Station, TX, USA) to further investigate any identified group differences. Due to the small sample size, these were considered exploratory analyses.

## **Results**

Among the 37 recruited subjects (mean age= 43.8 years, 89.2% female), cases (n=19) reported significantly higher levels of physical fatigue, pain, depression, anxiety and sleep disturbance

compared to the control group, although were comparable in terms of demographic and physiological parameters (table 1).

Overall, cases had mild SLE: only n=1 had a history of renal involvement and the mean SLICC score was 0.11 (SD 0.3). The majority experienced musculoskeletal (n=17) and/or cutaneous (n=12) involvement. The commonest prescribed immunosuppressant treatment was hydroxychloroquine (n=15), followed by methotrexate (n=8). Other SLE specific treatment at the time of study included azathioprine (n=2), mycophenolate mofetil (n=3) and rituximab (n=3). Only 3 patients were receiving long term prednisolone (5-8mg/day).

#### MRI Analysis

In assessment of calf muscle metabolic function, there was a difference ( $P = 0.045$ ) between the PCr half time recovery between SLE patients ( $33.0 \pm 9.0$  s) and healthy controls ( $27.1 \pm 6.6$  s). There were no significant differences in MD, RD or FA from DTI between SLE and controls (Table 2). Additionally, there were no significant difference in T2 ( $P = 0.185$ ) or fat fraction ( $P = 0.706$ ) between SLE (T2 of  $33.2 \pm 1.5$  ms, fat fraction of  $3.69 \pm 1.27$  %) and controls (T2 of  $32.6 \pm 1.1$  ms, fat fraction of  $3.90 \pm 1.81$  %) or in muscle cross sectional areas ( $P = 0.623$ ) (SLE:  $21.8 \pm 3.7$  cm<sup>2</sup>; controls:  $22.6 \pm 5.4$  cm<sup>2</sup>). The MR data from a healthy control is shown in Figure 1.

#### Within case correlations of PCr half time difference

There were no significant correlations identified between PCr half time and levels of physical fatigue:  $r = -0.28$  (95% CI -0.60-0.13),  $p = 0.25$  or mental fatigue  $r = 0.2$  (95% CI -0.21-0.54),  $p = 0.41$ .

#### Discussion

This is the first study of a rheumatological disease to investigate the relationship between skeletal muscle and fatigue employing multi-modal MR. Among fatigued SLE patients, calf muscle PCr recovery half time was significantly prolonged compared to non-fatigued healthy controls. These differences do not appear to be related to physical fatigue. Further, no differences in skeletal muscle microstructure were observed between cases and controls. Taken together, skeletal muscle does not appear to serve as a major factor in SLE related fatigue.

PCr recovery half time reflects the muscle oxidative capacity and is used as a marker of muscle mitochondrial function(37). In SLE there is accumulating evidence to support the presence of mitochondrial abnormalities in peripheral blood cells. For example, Gergely and colleagues observed hyperpolarised mitochondria in T-cells which resulted in greater ATP depletion, oxidative stress and ultimately cell death(38). We now provide supporting data that mitochondrial dysfunction might also exist within the skeletal muscle of patients with SLE. The same marker has previously been related to fatigue in SLE(39), although our exploratory analysis suggests that pathways other than skeletal muscle mitochondrial dysfunction may be involved in the generation of this symptom. Microstructural MRI of skeletal muscles has been applied in only a few clinical populations and, to our knowledge, never in the investigation of fatigue. DTI has evidenced changes of muscle integrity in athletes following marathon runs where standard sequences have failed to detect macroscopic differences(40). Furthermore, this method can distinguish disease activity in inflammatory muscle diseases with greater sensitivity than standard imaging(41). Among neuromuscular conditions, where existing clinical tests are inadequate to assess disease progression, the quantification of structural parameters such as muscle volumes and fat infiltration are providing superior biomarkers for clinical trials and practice(42). Such studies are similarly sized to the present investigation and so the absence of differences between our cases and controls in any of the sensitive microstructural metrics does not contradict the hypothesis that physical fatigue is related to structural abnormalities in SLE skeletal muscle.

If not skeletal muscles, what then are the main explanations of physical fatigue among SLE patients? A recent study of fatigue in another multi-system autoimmune disorder (ANCA associated vasculitis) failed to detect a significant relationship between physical fatigue and skeletal muscle mass (measured using dual-energy X-ray absorptiometry) or function. Compared to healthy controls, fatigued cases evidenced 1) reduced voluntary activation of skeletal muscle 2) reduced maximal voluntary contraction of skeletal muscle and 3) higher levels of perceived exertion - a finding that significantly correlated with physical fatigue(43). Together, these observations pointed towards centrally rather than peripherally driven mechanisms.

The novel application of cutting edge MR methods combined with a comprehensive approach to phenotyping are strengths of this study, however a number of limitations must also be considered. First, the highly selective eligibility criteria (purposely planned to enhance homogeneity by excluding known fatigue mechanisms) has resulted in a sample with generally mild disease. The results are therefore not generalizable to the wider disease spectrum. For example, patients with a history of myositis (prevalent in 4-16% of SLE cases(44)) were excluded. Data from this study cannot be used

to inform the usefulness of these methodologies in the evaluation of such manifestations (a distinct research question). Second, we recognise that SLE patients without fatigue would have served as a more precise control group. That said, given the pervasiveness of fatigue in this disease, it would have been logistically challenging to recruit such patients. Regardless, the absence of differences even with a healthy control group (as observed with almost all of the MRI metrics) indicates that these methodologies are unlikely to identify a clinically relevant fatigue specific signal. Uncertainty also exists regarding the clinical relevance of the statistically significant PCr measure since the 6s difference in recovery half time is lower in magnitude compared to other <sup>31</sup>P studies (for example, 18.7±0.9s in healthy controls vs 27.3±3.5s in diabetic patients (45); 35.0±3.0s in healthy controls vs 45.0±4.0s in patients with chronic obstructive pulmonary disease (COPD(46)). Third, although the sample size is equivalent to other MRI muscle studies, which have detected significant changes in other populations, we cannot be certain that larger sample sizes will not identify a significant effect. In particular, fully powered within case correlational analysis analyses, might uncover relationships between PCr and SLE fatigue. We suspect however that, in the absence of even a trend, any associations are unlikely to be major contributors to our understanding of physical fatigue.

This study provides evidence of feasibility for the use of multi-modal MRI muscle in patients with SLE. From this data, the investigation of physical fatigue would seem to be better served by examining alternatives to skeletal muscle based pathways. Learning from other chronic diseases, the investigation of central mechanisms using advanced MRI brain techniques appears to offer greater potential(47). Such approaches have been limited in SLE and should be encouraged in an effort to better understand this considerable patient challenge.

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**Conflict of interests:**

LP is an employee of GlaxoSmithKline. The authors declare no other conflicts of interest.

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## Tables

Table 1: Baseline characteristics



	Cases (n=19)	Controls (n=18)	P value
<i>Demographics</i>			
Age (years)	44.8 (14.43)	42.8 (13.6)	0.67
Female, n	17	16	0.95*
<i>Symptoms</i>			
Physical fatigue (CFS)	14.7 (3.6)	6.9 (0.6)	<0.0001
Anxiety (HADS)	9.3 (4.2)	4.3 (2.4)	0.0001
Depression (HADS)	6.7 (3.4)	1.6 (1.7)	<0.0001
Pain (NRS)	3.5 (2.3)	0.3 (0.8)	<0.0001
Sleep disturbance (JSS)	12.7(5.3)	4.8 (5.3)	<0.0001
<i>Physiological measures</i>			
VO <sub>2max</sub> <sup>#</sup> (ml/kg/min)	28.0 (4.4)	28.4 (6.0)	0.78
ESR (mm/hr)	18.7 (14.2)	13.6 (10.4)	0.28
Haemoglobin (g/L)	132.6 (11.2)	131.1 (6.9)	0.67
Creatinine (µmol/L)	69.7 (24.0)	64.2 (13.7)	0.39
Creatinine Kinase (U/L)	89.4 (34.2)	113.8 (71.3)	0.20

Summary statistics reported as mean (SD) and p values derived from t-tests unless otherwise stated

CFS – Chalder Fatigue Scale – physical domain; HADS – Hospital Anxiety and Depression Scale; NRS – Numeric Rating Scale 0-10; JSS – Jenkin’s Sleep Scale

\*derived from Chi<sup>2</sup> test; # derived from Siconolfi Step Test

Table 2: MR Results

	SLE	Healthy Controls	Independent Sample T-test	
	Mean ± SD	Mean ± SD	t-score	P-value
Metabolism <sup>1</sup>				
PCr Half Time (s)	33.0 ± 9.0	27.1 ± 6.6	2.087	0.045 *
End-exercise pH	7.00 ± 0.01	7.01 ± 0.01	0.704	0.488

Muscle Integrity <sup>2</sup>				
MD ( $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ )	1.57 $\pm$ 0.07	1.54 $\pm$ 0.12	0.850	0.401
RD ( $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$ )	1.39 $\pm$ 0.07	1.38 $\pm$ 0.11	0.597	0.554
FA	0.21 $\pm$ 0.02	0.21 $\pm$ 0.02	1.212	0.234
Muscle Condition <sup>3</sup>				
T2 (ms)	33.2 $\pm$ 1.5	32.6 $\pm$ 1.1	1.355	0.185
Fat Infiltration <sup>4</sup>				
Fat fraction (%)	3.69 $\pm$ 1.27	3.90 $\pm$ 1.81	-0.381	0.706
Size				
CSA ( $\text{cm}^2$ )	21.8 $\pm$ 3.7	22.6 $\pm$ 5.4	-0.497	0.623

Summary statistics reported as mean  $\pm$  standard deviation and p values derived from t-tests unless otherwise stated; \* - statistical significance

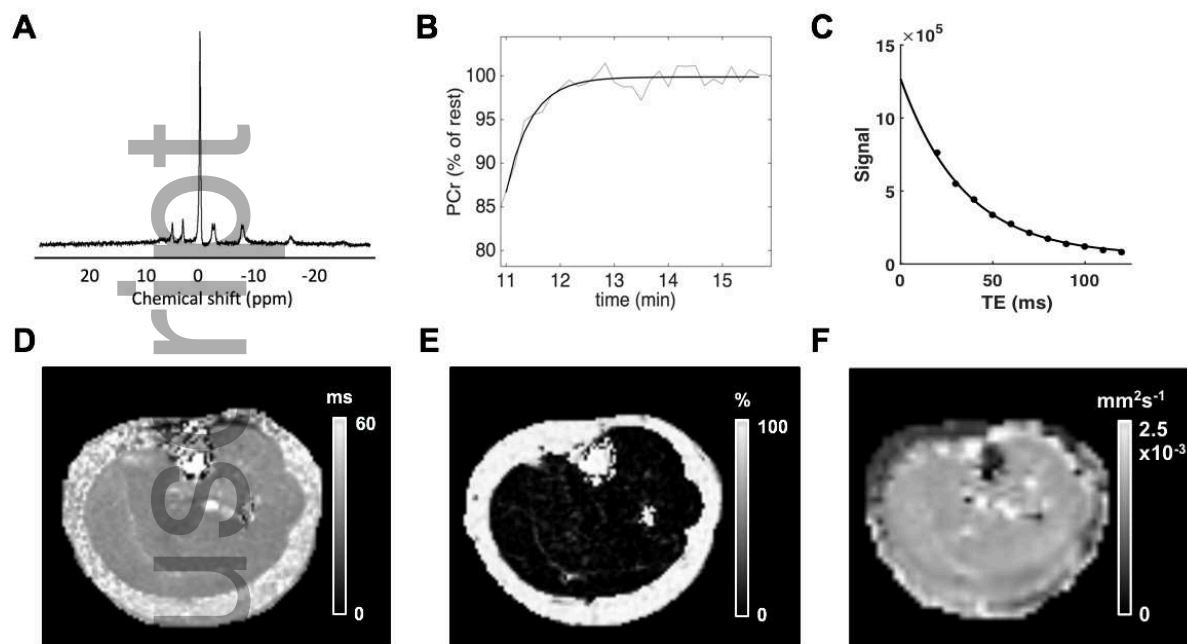
SLE – Systemic lupus erythematosus cases; PCr – phosphocreatine; MD – mean diffusivity; RD – radial diffusivity; FA – Fractional anisotropy; CSA – cross sectional area;

<sup>1</sup> One case and one control not analysed due to exercise non-compliance. Two cases and one control not analysed due to artifact in recovery curve.

<sup>2</sup> One control not analysed due to image artifact.

<sup>3</sup> Two cases and two controls not imaged due to image artifacts.

<sup>4</sup> One case and two controls not analysed due to flex-M coil use. One case not analysed due to image artifact.



**Figure 1: MR data from a healthy control.**

The baseline  $^{31}\text{P}$  spectrum (A) and the dynamics of phosphocreatine (PCr) during recovery period (B) are shown. The transverse relaxation from a single voxel within soleus muscle (C) is shown together with fitted curve. Calculated transverse relaxation time (T2) map (D), fat fraction map (E) and mean diffusivity (MD) map (F) are also shown.